NEUROLOGICAL CONSULTATIONS IN THE MEDICAL INTENSIVE CARE UNIT

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Critical care therapy has advanced over the past two decades, treating more patients and providing more complex care. However, the improved survival from septic shock, adult respiratory distress syndrome (ARDS), and multiple organ system failure results in critically ill patients facing a spectrum of new complications secondary to both illness and treatment. A third of intensive care unit (ICU) admissions have a neurological complication detrimental to outcome.[1] Neurological status (mainly depressed consciousness) is the major contributor to prolonged ventilation in a third of those who need it and is a significant factor in an additional 40%. Neurological complications double both the length of stay in hospital and the likelihood of death; the mortality rate for patients with neurological complications is 55% compared to 29% for those without. It is therefore unsurprising that neurologists are being increasingly called upon to review patients on the medical intensive care unit (MICU).

A neurological opinion is usually requested:

- to assess neurological manifestations of the primary disease process
- to evaluate the consequences of critical care therapy
- to offer a prognosis, or
- determine brain death.

The neurologist must approach these complex patients in a logical, meticulous, and sensitive manner. There are obvious inherent difficulties in reviewing on the MICU:

- difficulties in communication (sedation/endotracheal tube)
- bulky case records and numerous investigation results (scans often "off-site")
- a "Pandora's box" of ICU terminology (ARDS, SIRS, MODS, etc)
- unfamiliarity with types and levels of respiratory support, anaesthetic agents, and neuromuscular blockade
- limitations of the clinical examination caused by sedation or neuromuscular blockade
- constraints in arranging further investigations (for example, availability of neurophysiology or ventilator/magnetic resonance imaging (MRI) compatibility)

TERMINOLOGIES

The terminologies used on the ICU are formidable and often ill understood by the consulting clinician. Knowledge of the taxonomy of sepsis and allied syndromes is essential in appreciating their neurological implications. We define here the most important terms with their significance. Septic shock is the most common cause of death on the ICU, though the specific infection is identified on culture in only 30–50% of cases.

The sepsis syndromes (table 1) represent a spectrum of clinical illness from systemic inflammatory response syndrome (SIRS) through organ dysfunction to multiple organ failure to death caused by immune responses to infection, and characterised by systemic inflammation. SIRS consists of alterations in physiological variables induced by infection. Sepsis is SIRS in the presence of documented infection. Severe sepsis is defined as sepsis with end organ dysfunction or hypoperfusion. Septic shock is sepsis associated with hypotension despite adequate resuscitation (intravenous fluids, inotropes, vasoactive agents, and specific treatment), together with perfusion abnormalities (lactic acidosis, oliguria, acute alteration in mental status). Organ dysfunction refers to inadequate function of kidneys, lungs, gut, liver, skin, heart or central nervous system. The multiple organ dysfunction syndrome (MODS) or multiple organ system failure is defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

The inflammatory mediators released in the sepsis syndromes make them the most likely cause of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Altered integrity of the alveolar–capillary membranes leads to non-cardiogenic pulmonary oedema, resulting in hypoxaemic respiratory failure and ALI, the severe form of which is ARDS.

The mortality rate in SIRS is approximately 7%, in sepsis 16–20%, and in septic shock 45%.

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Table 1 Definition of sepsis syndromes

Systemic inflammatory response syndrome (SIRS)
Defined by the presence of two of the following
- Temperature >38°C or <36°C
- Heart rate >90 per minute
- Respiratory rate >20 breaths/min or $PaCO_2$ < 32 mm Hg (4.3 kPa)
- White cell count >12000 or <4000 cells/mm^3, or >10% immature forms

Sepsis
SIRS with evidence of infection

Severe sepsis
Sepsis associated with:
- Organ dysfunction
- Hypotension (systolic pressure <90 mm Hg or fall >40 mm Hg)
- Hypoperfusion (manifest as lactic acidosis, oliguria, altered mental state)

Refractory shock
Shock refractory to conventional treatment (fluids, inotropes, vasoactive agents) within 1 hour

Multiple system organ failure
The presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (The 1994 Consensus Conference definition)

► Onset	Acute and persistent
► Oxygenation criteria	$PaO_2/FiO_2 \leq 300$ for ALI
	$PaO_2/FiO_2 \leq 200$ for ARDS
► Exclusion criteria	PAOP ⩾18 mm Hg
	Clinical evidence of left atrial hypertension
► Radiographic criteria	Bilateral opacities consistent with pulmonary oedema

ASSESSMENT AND EXAMINATION

Neurological evaluation of the MICU patient is challenging. Cursory assessment and attribution of problems to critical illness itself or to some vague notion of a "multifactorial" insult must be avoided. An opinion should be formulated as a result of a detailed study of antecedent events, charts, investigations, and a targeted examination often limited by concomitant treatment. Before consultation, sedation and muscle relaxants should, where possible, be withdrawn allowing a sufficient time (depending upon half life and prolongation by deranged metabolism) to "lighten" the patient for examination. Charts should be reviewed for evidence of infection, organ dysfunction, current treatment, and progress. All scans should be seen and, when appropriate, reviewed with radiology colleagues. A reprise of current illness presentation and past history directly from a family member or partner is desirable. The presence of a member of the ICU team during the consultation is essential.

General examination

While others will have done this before, the emphasis on life support can result in evolving signs being overlooked. The skin may give important clues such as splinter haemorrhages (endocarditis), ecchymoses (bleeding disorder), spider angiomata/gynaecomastia (hepatic encephalopathy) or a petechial eruption on the chest (fat emboli).

Mental status

This involves assessment of arousal (level of consciousness), sensorium (content of consciousness), and motivation. Evaluation of coma and confusion has been addressed in an earlier supplement (issue 3: sleep and coma). Impaired motivation may result in "psychogenic" unresponsiveness. Here eyes may resist voluntary opening and, when released, close rapidly rather than with the normally anticipated slow incomplete closure. The discrepancy between apparent alertness and immobility can be a clue to the presence of akinetic mutism. Alternatively, patients who are "locked in" (for example, central pontine myelinolysis), while awake, cannot (through quadriparesis and bulbar palsy) produce purposeful cranial, truncal or limb movements. Frontal release phenomena, forced grasping, and perioral primitive reflexes (snout and pout, etc) are found in both diffuse structural and metabolic disease, and asymmetry of the grasp reflex may suggest unilateral weakness. Assessing the level of consciousness in the intubated patient is problematic. A continuous performance test (patient is asked to raise the hand every time he or she hears a certain letter in a standardised sentence) and the three consecutive hand position test ("thumbs-up/fist/victory sign") have been evaluated to monitor alertness (continuous performance) and praxis (hand position).[2] This potential adjunct to the Glasgow coma score (GCS) allows assessment of patients when the verbal and eye responses cannot be reliably tested, but its utility is limited by requiring intact upper limb function.

Pupils and eye movements

Asymmetry or alteration in size and response suggests structural disease and may aid localisation. Reactive responses with disordered arousal suggest a metabolic disorder. However, anoxia can result in unreactive pupils of varying sizes (pinpoint, mid position to large). While the eyelids are usually closed in coma, tonic lid retraction and reopening following forced closure occurs with pontine disease. Blinking may result reflexly in response to illumination or touch. A failure to blink or a widening of the palpebral fissure suggests facial weakness, as does a Bell's phenomenon, without eye closure, in response to corneal stimulation. The corneal reflex (testing the integrity of Vth and VIIth cranial nerves) is depressed proportional to the depth of coma. Patients should be examined for roving eye movements and other spontaneous movements (for example, ocular bobbing), gaze palsies, and internuclear ophthalmoplegia. Oculocephalic manoeuvres

and oculovestibular testing should be carried out as part of the brain stem assessment.

Careful examination of the pupils, eyelids, and eye movements will provide valuable information on causation, localisation, and even prognosis.

Motor examination

Posturing, spontaneously or in response to pain, forms an important item of the GCS. Flexor and extensor postures are variably encountered in metabolic coma (hypoxic–ischaemic, hypoglycaemic, hepatic and uraemia). While the type of posture (extensor or flexor) may predict outcome in trauma, this is importantly not so with metabolic disease. Weakness is difficult but important to evaluate. When present it may reflect level of arousal, focal hypoxic ischaemic damage, lack of motivation, akinetic mutism, "locked-in" state, or spinal cord, peripheral nerve, muscle or neuromuscular junction disturbance. The pattern and distribution of weakness with its concomitant reflex changes and plantar responses serve as vital localising clues. Remember that agents causing neuropathic disturbance and neuromuscular blockade, besides sympathomimetic and anticholinergic agents, may influence reflex state.

Myoclonus indicates a metabolic disease (usually hypoxic–ischaemic where it may be massive, bilateral and drug refractory). Seizures may be subtle and close attention should be paid to any repetitive movements that might represent non-convulsive status.

Sensory examination

Although often unreliable in the context of fatigue and poor attention, it should not be abandoned completely as important clues to central or peripheral localisation will be missed.

At the conclusion of assessment and examination the neurologist should be able to address the following important questions:

- Localisation—central or peripheral?
- Structural or metabolic/infective?
- Caused or obscured by current treatment?
- Is a diagnosis possible or are further investigations required?
- Is it possible, at this stage, to predict short and long term outcome?

CLINICAL SCENARIOS

In their study of neurological complications in the MICU, Bleck and colleagues[3] identified metabolic encephalopathy in 28.6% of cases, seizures in 28.1%, hypoxic–ischaemic encephalopathy in 23.5%, stroke in 22.1%, and other neurological diagnoses in 23%. Patients often had multiple complications.

Common clinical scenarios are:

- a failure to awaken/depressed conscious state
- seizures or odd movements
- weakness and difficulty weaning from ventilator
- predicting prognosis
- determination of brain death.

FAILURE TO AWAKEN/DEPRESSED CONSCIOUSNESS

Sudden or gradual deterioration in consciousness may occur during MICU stay or reflect failure to awaken after general anaesthesia. This may be the result of several potential causes (box 1).

Box 1 Causes of failure to awaken in the MICU

- Sedative agents and their altered metabolism
- Infection and sepsis
- Anoxic–ischaemic injury
- Renal impairment and uraemia
- Hepatic impairment
- Central pontine myelinolysis
- Cholesterol microembolisation
- Ischaemic stroke
- Multifactorial—most often

Sedation and analgesia are confounding factors in those with depressed consciousness. These drugs are used to reduce agitation and pain, with the goals of diminishing discomfort, oxygen demand, ventilator asynchrony, and self removal of catheters and other devices. They also induce amnesia and reduce the risk of a post-traumatic stress disorder.

Withdrawal of sedation before review is essential for reliable neurological assessment. It will also eliminate the temptation to attribute depressed consciousness to sedation alone. Drugs must be reviewed with attention to altered metabolism and potential interactions. The properties and factors influencing common anaesthetic agents are listed in table 2.

Special mention is made of propofol, which is generally thought to be free from renal and hepatic influences. Propofol does accumulate after prolonged administration and requires a washout period.

Besides sedation, the most common cause of depressed consciousness is a *metabolic encephalopathy.* Several situations lead to interruption in the delivery of energy substrates to the brain (hypoglycaemia, hypoxia, ischaemia) or to altered neuronal excitability (hepatic and renal failure, hyperosmolarity, electrolyte imbalances, hypercapnia), resulting in an altered mental state. More than one factor may be implicated. A thorough review of the temporal sequence of events is needed, with special attention to the timing of specific metabolic insults and the onset of encephalopathic features. Therapeutic interventions, progress charts, administration of sedation, and trends in metabolic parameters need to be analysed. Cause and effect relationships may be difficult to establish, especially where encephalopathy is of a multifactorial nature.

Septic encephalopathy is the most common type of metabolic encephalopathy encountered in the MICU, and is defined as an encephalopathy in the presence of sepsis and in the absence of other obvious causes. Sepsis and end organ dysfunction accompany delirium and depressed consciousness. Cause appears closely related to the cytokines released in sepsis (procalcitonin, tumour necrosis factor α (TNFα) and interleukin 6 (IL-6)). These lead to altered cerebral haemodynamics, disruption of blood brain barrier, cerebral oedema, and disturbed neuronal function. Treatment is directed at the source of sepsis and prognosis is poor.

Uraemic encephalopathy may be either acute (more often) or chronic. Again, it is essential to establish a link between the clinical presentation of encephalopathy and the onset, severity, and rate of progression of deranged renal function. Other potential contributing factors must also be considered. Asterixis, tetany, and myoclonus are common. *Dialysis disequilibrium* occurs after instigation of dialysis. Features include postural headache, hypertension, occasionally cortical blindness, and seizures. It is self limiting (settling in hours) and attributed to transient cerebral oedema, secondary to the

Table 2 Properties of sedatives commonly used in the MICU

Anaesthetic agent	Onset after intravenous administration	Metabolism	Half life of parent compound	Prolonged action with:
Diazepam	2–5 minutes	Liver	20–120 hours	Liver disease Renal disease
Midazolam	2–5 minutes	Liver	3–11 hours	Liver disease Renal disease Propofol Macrolides Diltiazem P450 inhibitors
Lorazepam	5–20 minutes	Liver	8–15 hours	Liver disease Renal disease
Haloperidol	3–20 minutes	Liver	18–54 hours	Liver disease
Propofol	1–2 minutes		26–32 hours	Infusion >12 hours

slower clearance of urea from the brain as compared to blood, thus establishing an osmotic gradient.

Hepatic encephalopathy may be either acute or acute on chronic. The diagnosis is made on temporal association between deranged liver function and encephalopathic illness and ruling out other factors. Asterixis (a flapping tremor) is a non-specific finding and not pathognomonic. Fulminant hepatic failure leads to cerebral oedema, whereas chronic hepatic encephalopathy is caused by accumulation of substances secondary to liver failure and portal–systemic shunting (for example, endogenous benzodiazepines). Mannitol, hyperventilation, and high dose barbiturates may be useful in acute encephalopathy. Steroids and haemofiltration are ineffective.

Anoxic–ischaemic encephalopathy is common in the MICU, though it is also commonly encountered after major surgery. It should be diagnosed only where there is clear documentation of hypoxic and/or hypotensive insult preceding the onset, and in the absence of other obvious confounding factors. A discrete episode of profound hypotension or hypoxia is not essential, as subtle sustained hypotension or hypoxia may have deleterious effects on the already disturbed cerebral haemodynamics in the MICU patient. The degree of clinical impairment is often related to both severity and duration of hypoxic insult. Review of all blood pressure and oxygenation readings is essential. Useful clinical pointers include myoclonic jerks, pupillary changes, and unusual patterns of weakness ("man in a barrel") from watershed injury. Movement disorders may rarely result from basal ganglia damage. *Delayed post-anoxic encephalopathy* is characterised by a lucid interval (1–4 weeks) between insult and the encephalopathy. Here diffuse hemisphere demyelination is associated with cognitive impairment, associated with cerebellar and pyramidal disturbance. Progression to coma and death occurs.

With *central pontine myelinolysis*, rapid changes in plasma sodium and osmolarity produce on imaging the typical "bat wing" appearance of pontine demyelination (fig 1). Demyelination can be predominantly extra pontine (25%). Presentation is with impaired conscious level, brain stem signs, and limb weakness.

In the case of *cholesterol embolisation*, rapid neurological deterioration, leading to MICU admission, can occur precipitously after an angiographic procedure. A diffuse encephalopathy results, often with evidence of systemic embolisation. Retinal haemorrhages, renal failure, livedo reticularis, and a petechial rash develop. Muscle biopsy has a high diagnostic sensitivity showing the presence of stacked needle shaped cholesterol crystals. Fat embolism can produce a similar presentation following trauma or orthopaedic procedures.

Failure to awaken may be caused by intracranial infarction or haemorrhage—*stroke*. Watershed infarction results from globally reduced cerebral perfusion. Multiple simultaneous territorial infarcts can result from cardiac thrombus, aortic arteriosclerosis or infective endocarditis. Venous infarction may complicate systemic infection, especially when accompanied by dehydration and a hypercoagulable state. Haemorrhage can result from coagulopathies (for example, disseminated intravascular coagulation), mycotic aneurysms, and thrombocytopenia. Cranial imaging (time dependent) is diagnostic.

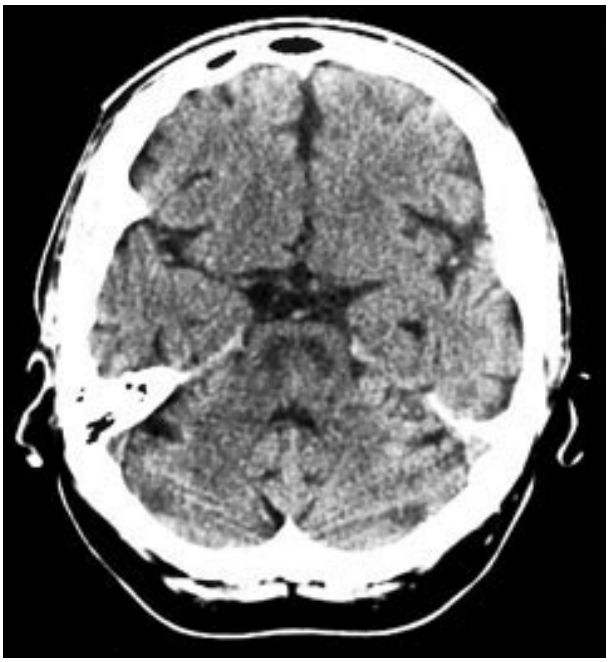

Figure 1 Computed tomographic (CT) scan demonstrating the typical "bat wing" appearance of central pontine myelinolysis in a patient recovering from depressed consciousness with accompanying electrolyte derangement.

Box 2 Common causes of seizures in the MICU

- Anoxia–hypoxia
- Electrolyte disturbances
- Drugs:
  - antibiotics: imipenem, quinolones (for example, ciprofloxacin), penicillins
  - bronchodilators: theophyllines, aminophylline, terbutaline
  - antiarrhythmics: lignocaine, flecainide
  - immunosuppressants: cyclosporine, FK506, OKT3
- Stroke
- Alcohol withdrawal
- Narcotic agent withdrawal
- Hypoglycaemia/hyperglycaemia

Parameters to monitor

- Sodium, potassium, and renal function
- Calcium
- Magnesium
- Blood sugar—high and low
- EEG—often difficult

SEIZURES

Seizures on the MICU are usually focal or generalised motor convulsions, though all seizure types occur. Common precipitants are hypoxia/ischaemia, drug toxicity, narcotic withdrawal, and metabolic abnormalities (box 2). Diagnosis of seizure type and cause are important to ensure early appropriate treatment and differentiation from myoclonus and movement disorders secondary to basal ganglia injury. Most seizures occur singly, and recurrence is usually prevented by initiation of anticonvulsant treatment. Subtle movements of fingers, eyes or lips may indicate non-convulsive status (NCS), found in 8% of ICU patients.[4] NCS should be considered where there is abrupt deterioration in conscious level without explanation, often following a recognised seizure or after anoxic ischaemic insult with preserved brain stem reflexes. Convulsive status is less common. Status of either kind must be treated promptly to avoid further brain injury (see Shorvon in issue 2 of this series[5]).

The Lance-Adams syndrome (post-anoxic action myoclonus) is seen after hypoxic brain injury, especially following cardiac resuscitation. Myoclonic jerks become evident as consciousness is regained. Response to benzodiazepines, piracetem or valproic acid is usual.

Myoclonic status occurs within 12 hours of cardiac resuscitation and persists for a further 48 hours. These patients are deeply unconscious with jerking movements involving limbs and face (grimacing and eye opening) that are typically unresponsive to drug treatment. EEGs show "burst suppression" changes and imaging a loss of grey matter–white matter differentiation, with or without watershed infarction (figs 2 and 3). Myoclonic status is a poor prognostic sign predicting death or vegetative state in 90% of cases. Absolute prognostication is difficult, as is the decision to maintain life support. Somatosensory evoked potentials (SSEPs) may help but are not always available. The severity of imaging findings usually guides decision making.[6]

Investigations of encephalopathy and seizures

Despite many pointers to a metabolic cause, structural brain lesions require exclusion. Imaging is essential. MRI is superior to computed tomography (CT) in showing the early and subtle changes of infarction, infection, and ischaemia. Not all MRI scanners are ventilator compatible and patients must be stable and specific treatments in place before transfer to the imaging suite. EEG (continuous monitoring if available) may be invaluable, especially in status epilepticus and non-convulsive status. Evoked potential testing is available in few MICUs despite some evidence that SSEPs may contribute to predicting outcome in anoxic encephalopathy.

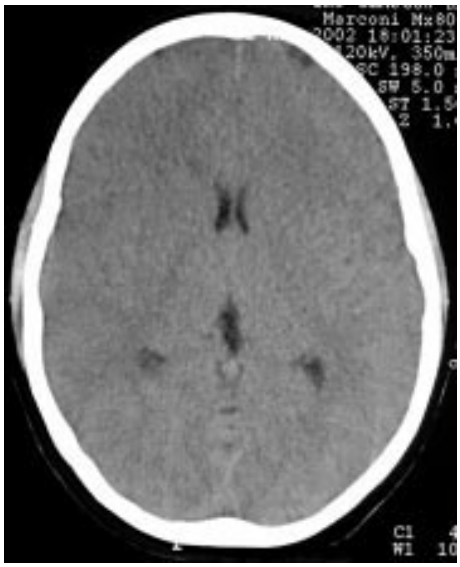

Figure 2 CT scan of an 18 year old girl with hypoxic encephalopathy secondary to an attack of acute severe asthma. There is generalised loss of differentiation between grey and white matter with some swelling consistent with diffuse hypoxic brain injury.

WEAKNESS

Weakness on the MICU commonly manifests as difficulty in "weaning" from ventilation, paucity of movements in an obtunded patient, or generalised or focal weakness in an alert patient. It must be distinguished from the non-specific weakness of fatigue secondary to systemic illness.

Weakness may be caused by central or peripheral causes. In the comatose patient, a central cause is more plausible, whereas a peripheral explanation (nerve, muscle, neuromuscular junction) is more likely in a more alert individual. Weakness is generalised or focal. While hemiparesis is more likely to be caused by cerebrovascular complications, paraparesis is usually due to nerve or muscle disorders, and less often spinal disorders (infarction secondary to a hypotensive or embolic episode). Monoparesis may occasionally be a manifestation of a stroke, or more usually the result of pressure or positioning palsy (femoral or common peroneal nerve palsies).

The neurologist should be aware of the types of neuromuscular blockade on the MICU (table 3). These facilitate intubation and mechanical ventilation, and reduce fluctuations in intracranial pressure. Succinylcholine depolarises the neuromuscular junction, rendering it refractory to acetylcholine. All other agents are non-depolarising and attach themselves to the motor end plate, blocking activation by acetylcholine. Both types of blockade facilitate each other. Succinylcholine can precipitate malignant hyperthermia. Non-depolarising agents induce histamine release, hypotension, and bradycardia.

Several other agents interfere with neuromuscular transmission, by influencing calcium ion fluxes at nerve terminals. These include:

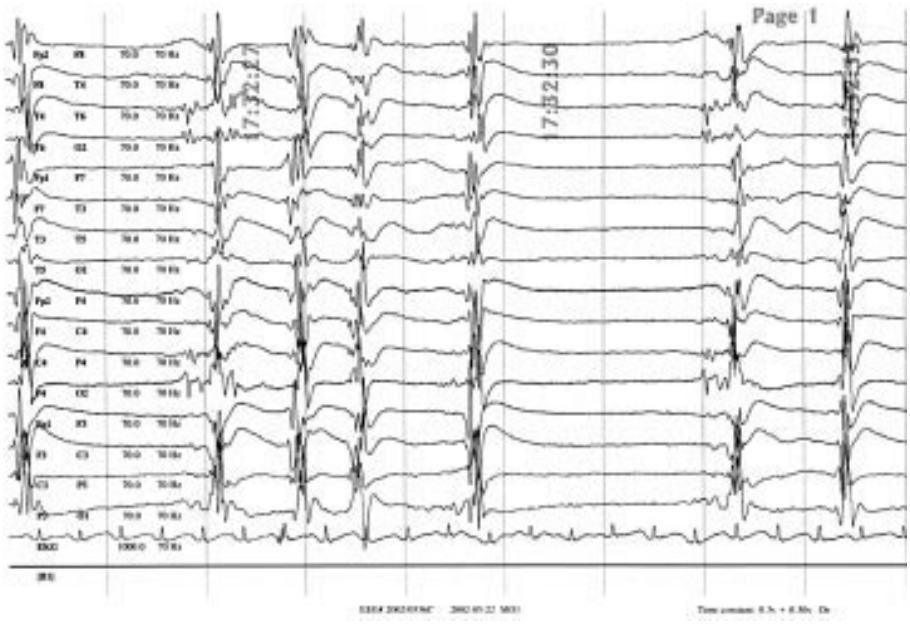

Figure 3 Severe hypoxic encephalopathy on EEG 24 hours after cardiorespiratory arrest in the same patient as fig 2, demonstrating subtle clonic movements. The EEG was unmodified by thiopentone or lorazepam given later during the recording.

Table 3 Properties of commonly used neuromuscular agents

Name	Nature	Primary excretion	Time to recovery	Interactions
Succinylcholine	Depolarising	Plasma cholinesterase	11 minutes	Aminoglycosides
Pancuronium	Non-depolarising agents	Renal	50 minutes	Renal failure
Vecuronium		Liver	56 minutes	Metabolic acidosis
Atracurium		Hoffman degradation	52 minutes	Hypermagnesemia
Doxacurium		Renal	116 minutes	Inhaled anaesthetics

- aminoglycosides
- colistin
- streptomycin
- polymyxin B
- tetracyclines
- D-penicillamine.

Lambert-Eaton myaesthenic syndrome can first present in the MICU with neuromuscular weakness as a consequence of disease related reduction of nerve terminal calcium influx exacerbated by drugs that alter calcium flux.

Neuropathies

The critical care patient runs the risk of developing several forms of polyneuropathy (box 3), the most common being critical illness polyneuropathy (CIP). However, other causes such as therapeutic agents and nutritional issues must be considered. Guillain-Barre syndrome and acute intermittent porphyria are rarely encountered but should be borne in mind.

Critical illness polyneuropathy

Critical illness polyneuropathy (CIP) is defined as a predominantly motor axonal polyneuropathy with acute onset in a setting of SIRS and with multi-organ dysfunction. It typically develops in the context of prolonged ICU stay (> 7 days) and in 40–70% of patients with sepsis/SIRS and MODS[7] and should not be diagnosed when these are absent. Additional risk factors include age, hypoalbuminaemia, hyperglycaemia, and insulin deficiency (a clinical state in which glucose tolerance is likely to be impaired). Clinical features may vary, especially with respect to the degree and extent of limb involvement (box 4).

Pathophysiology is complex and incompletely understood. Disturbances in the microcirculation with cytokine (TNFα and IL-6) induced increased vascular permeability, autotoxins and neurotoxic serum factors are postulated and humeral factors have been identified. There is no clear relation between CIP and concomitant drug treatment. Nerve morphology shows axonal degeneration without evidence of an inflammatory/vasculitic response. CIP is associated with higher mortality and leads to prolonged rehabilitation.[8] There is no specific treatment other than that of sepsis and continued ventilatory support. An intensive insulin regimen is known to reduce the risk of CIP and intravenous immunoglobulin, and nerve growth factors have potential for the future. The role of the

Box 3 Acute polyneuropathies in the MICU

- Critical illness polyneuropathy (CIP)
- Guillain-Barre syndrome
- Antibiotics:
  - metronidazole
  - penicillins
  - aminoglycosides
  - isoniazide
- Infections:
  - mycoplasma
  - meningococcus
- Acute intermittent porphyria
- Phosphate deficiency
- Vitamin deficiencies
- Chemotherapy

Box 4 Clinical features of critical illness polyneuropathy

- Presence of SIRS, MODS
- Sparing of cranial nerves
- Limb weakness, distal > proximal
- Diminished reflexes (can be elicited in 50%)
- Muscle wasting (may be prominent)
- Glove and stocking loss of pinprick sensation
- Axonal damage with reduced compound muscle action potentials with prolonged distal latency
- Associated with poorer prognosis (concomitant MODS and sepsis), prolonged recovery, and rehabilitation[8]
- Fair recovery of neuropathy if patient survives

neurologist is that of recognising this disorder and its likely need for prolonged ventilation, physiotherapy, and rehabilitation.

Muscle problems

Critical illness myopathy (CIM) is an increasingly identified MICU myopathic syndrome. Patients have usually been administered neuromuscular blockade as well as steroids. Steroids are potent inducers of some forms of cytochrome P450, which are associated with skeletal muscle sarcoplasmic reticulum. Induction of P450 enzymes results in the formation of reactive metabolites and activation of calcium release channels leading to muscle injury. Differences between muscle fibre types in calcium handling may explain preferential injury to type 2 fibres. The prognosis in CIM is generally good and treatment supportive. Three distinct forms of CIM are recognised (box 5). Myopathy may also result from cachexia or, rarely, rhabdomyolysis (painful weak muscles with grossly elevated muscle enzymes and myoglobinuria).

Occasionally previously undiagnosed muscle disease can become evident when a patient is in the MICU for other reasons. Any muscle disease that can produce respiratory muscle weakness can lead to failure to wean, myotonic dystrophy being the most common (see section on non-invasive ventilation).

Box 5 Variants of critical illness myopathy

Critical illness myopathy (common)
- Aetiology unknown
- Associated with steroids, neuromuscular blockade, sepsis, and MODS
- Weakness, paresis or failure to wean
- Diffuse non-necrotising myopathy
- Fibre atrophy, fatty degeneration, and fibrosis
- Creatine phosphokinase values normal

Thick filament myopathy
- Associated with steroids and neuromuscular blockade
- Typically in status asthmaticus and organ transplantation
- Selective loss of myosin filaments
- May progress to necrosis
- Possibly an early stage of acute necrotising myopathy

Acute necrotising myopathy
- Associated with neuromuscular blockade and large doses of steroids
- Typically in status asthmaticus
- Prominent myonecrosis
- Raised creatine phosphokinase
- Good outcome

Investigating suspected neuromuscular disease

Neurophysiology should be sought where possible. Needle electromyogram (EMG) cannot distinguish myopathy from neuropathy and may even mislead. Muscle biopsy is the best method for diagnosing myopathy and should be considered in weak patients whose history/background does not fit with CIP. Serum creatine kinase can be normal despite an overtly "myopathic" biopsy, or misleadingly elevated because of non-specific muscle injury (for example, intramuscular injection).

OFFERING A PROGNOSIS

This is never straightforward and especially so in the MICU. The aim is to confidently identify patients with a poor prognosis and to prevent the inappropriate continuation or institution of resuscitative measures. Difficulties and constraints include the limited data available, the absence of prospective studies, and the presence of multiple variables that influence outcome in critically ill patients. It must be emphasised that current literature is far from adequate and that it is too much to expect literature to replicate the many permutations and combinations that confront the physician. A pragmatic approach is required with each patient being evaluated on an individual basis. A complete review of the history, possible factors contributing to coma, treatment measures, and further therapeutic options is essential. Somatosensory evoked potentials (where available) may be useful in prognostication, in that their absence in anoxia indicates a poor outcome.

It must be remembered that approximately half of patients respond acutely to resuscitation after cardiopulmonary arrest, but only 15% survive to discharge from hospital. If cardiopulmonary resuscitative measures take more than 15 minutes, mortality is greater than 95%. With measures longer than 30 minutes, survival is improbable. Absent motor and pupillary responses at 72 hours, absent bilateral SSEPs, and a burst suppression EEG are each 100% specific in predicting death or persistent vegetative state, but with wide ranges in sensitivity and small but significant false positive rates.[9]

The following features may serve as a guide:

- *Aetiology of coma*—Patients with metabolic encephalopathy or drug/toxin overdose are more likely to do well as compared to those with stroke and hypoxic–ischaemic injury.
- *Depth of coma*—The lower the level of consciousness, the worse the outcome. However, accurate assessment is difficult because of influence of drugs, uraemia, and sedation.
- *Duration of coma*—The longer the duration of coma, the less the likelihood of a good outcome. Again, it is difficult to know when exactly a patient slipped into coma, as most patients would be on sustained sedation for long periods of time. Certainly, the longer sedation has been deployed, the greater the time allowed for a patient to wake up.
- *Clinical signs of disturbed brainstem function*—Absent pupillary and corneal reflexes indicate a poor outcome. An absence of caloric tests, doll's eye movements, and motor responses contributes further. However, as always the influence of concomitant treatment must be taken into account.

DETERMINING BRAIN DEATH

Neurologists are asked to review patients and diagnose brain death in two situations—if the possibility of organ donation exists, and when withdrawal of artificial life support is considered. These are both delicate issues and must be approached with appropriate sensitivity. Speaking personally to the family and discussing all issues is mandatory.

Learning points

- Personal review of history, presentation, and investigations is a must
- All therapeutic agents must be scrutinised with an eye on altered metabolism and possible interactions
- Understanding of sepsis and allied syndromes is essential for the recognition of their neurological manifestations
- Only attribute illness to multifactorial insults after careful analysis of the multiple factors
- Consult with other specialities when appropriate

Brain death is defined as the irreversible cessation of all brain function, including the brainstem. The clinical diagnosis of brain death is equivalent to irreversible loss of all brainstem function. The four essential elements of brain death are loss of consciousness, the absence of motor responses and brainstem reflexes, and apnoea. In the great majority of patients, imaging will display an abnormality, which explains loss of brain and brainstem function. Wijdicks[10] reviewed criteria in 80 countries finding major differences in diagnostic procedures. The UK Department of Health[11] and American Academy of Neurology guidelines[12] for the diagnosis of brain death are summarised below.

The diagnosis of brain death is clinical (an EEG is not required)

(1) Cause of brain death must be specifiable and irreversible
(2) Exclude effects of central nervous system depressant agents (tranquillisers, hypnotics, narcotics, other toxins) and neuromuscular blockade
(3) Potentially reversible circulatory, metabolic, and endocrine disturbances must be excluded as the cause of continuation of unconsciousness
(4) Hypothermia must be excluded as the cause of unconsciousness
(5) All brain stem reflexes must be absent:
  (a) Pupils fixed and usually dilated (exclude effects of local and systemic agents)
  (b) Absent corneal reflexes (avoid local trauma while testing)
  (c) Absent gag reflex or no response to tracheal suctioning
  (d) Absent vestibulo-ocular reflex (cold caloric test). After ensuring that tympanic membranes are intact, inject 50 ml of ice cold water into each ear with the head flexed at 30°. Observe for one minute. Test other side after a gap of five minutes. Eye movements must be completely absent
  (e) Absent oculocephalic reflexes (doll's eye movements)
  (f) No motor response in the distribution of the cranial nerves to any form of stimulation
(6) Absence of spontaneous respiration after:
  (a) Pre-oxygenation with 100% oxygen for 10 minutes
  (b) Disconnection of ventilator
  (c) Administration of 100% oxygen (6 litres/min) to maintain oxygenation
  (d) Ensuring $P_{CO_2} > 60$ mm Hg
  (e) Observation for spontaneous respiration for 10 minutes
  (Note: if bradycardia or arrhythmia occur the ventilator must be reconnected and other means used to diagnose brain death)

Two licensed and experienced physicians (who are not members of a transplant team) must examine and document irreversible and total cessation of brain function. The findings, which led to this conclusion, must also be documented.

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